

infectio

SUPLEMENTARY ONLINE MATERIAL

Colombian consensus on the diagnosis, treatment and prevention of *Candida* Spp. disease in children and adults^{*,+}

Annex 1. Vote on questions of the modules of the consensus (Delphi methodology).

Module	No. of Voters	Mean	Median	Minimum Scored Value	Maximum Scored Value	Percentage of Applicability
DIAGNOSIS OF INVASIVE CANDIDIASIS (IC)	13	7.3	7	3/1	9/9	77
DIAGNOSIS OF CANDIDEMIA	13	7.2	7	2/1	9/9	88
ANTIFUNGAL PROPHYLAXIS FOR CANDIDEMIA/IC	11	7.0	8	1/1	9/9	95
CANDICEMIA/IC IN NON-NEUTROPENIC PATIENTS	13	6.3	7	3/1	9/9	94
CANDICEMIA/IC IN NEUTROPENIC PATIENTS	13	6.8	7	2/1	9/9	95
TARGETED ANTIFUNGAL TREATMENT FOR CANDIDEMIA/IC	13	6.8	7	2/1	9/9	95
CANDICEMIA/IC IN NEONATE PATIENTS	9	8.4	9	3/1	9/9	100
MANAGEMENT OF CANDIDEMIA/IC IN SPECIAL SITUATIONS	13	6.5	7	2/1	9/9	90
INTRAABDOMINAL/PERITONEAL IC	13	6.5	7	2/1	9/9	94
Candida spp. URINARY TRACT INFECTIONS	13	6.7	7	2/1	9/9	94
Candida spp. RESPIRATORY TRACT INFECTION	13	6.7	7	2/1	9/9	94
PREVENTION OF Candida spp. IFDs	9	9.0	9	9/9	9/9	100

Annex 2. Score of guidelines found in the bibliographical search by AGREE II methodology^{38,40,42,46,70,72,108,178,388-392}.

MODULE		Bibliographical References											
MODULE	1	2	3	4	5	6	7	8	9	10	11	12	13
MODULE 1 : Scope and Objectives	81.6	75.3	70.6	80.6	80.6	71.5	75.9	72.2	78.4	48.5	75.0	73.6	80.6
MODULE 2 : Participation of persons involved	56.4	48.5	55.6	56.3	60.2	68.1	69.8	66.7	67.9	49.0	54.2	52.8	55.6
MODULE 3 : Rigor of Evaluation	62.0	40.0	45.8	87.5	58.3	65.9	75.9	64.8	76.6	47.9	60.9	60.4	59.9
MODULE 4 : Clarity of the Presentation	87.6	79.3	85.7	92.1	88.9	77.1	90.1	85.8	88.9	86.4	93.1	97.2	91.7
MODULE 5: Applicability	30.1	31.1	36.9	46.4	55.6	30.2	41.7	49.5	52.8	37.5	33.3	17.7	27.1
MODULE 6: Editorial Independence	64.7	65.9	90.5	99.4	55.6	100.0	100.0	100.0	86.1	75.8	100.0	100.0	100.0
NUMBER OF EVALUATORS	13	11	7	14	6	8	9	9	9	11	4	4	4
TOTAL MEAN	61.9	51.5	57.9	77.0	64.7	65.1	73.1	69.2	74.0	53.8	64.7	62.0	63.9

Annex 3. Table of Authors' affiliation

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Abbreviation	Conflict of interest disclosed:	Sponsor:
OL	He was a speaker and received scientific sponsorship.	Pfizer S.A.S, Merck Sharp and Dohme (MSD). 2016-2017
PR	She was a consultant and speaker, and received research funding and scientific sponsorship.	Pfizer S.A.S, Merck Sharp and Dohme (MSD). Colombia /Latin America 2016-2017
СНР	He was a consultant and speaker, and received research funding and scientific sponsorship.	Pfizer S.A.S, Merck Sharp and Dohme (MSD), Merck Colombia, Amarey Nova medical, Biomerieux, Novartis, Abbott-Lafrancol, Takeda. Colombia /Latin America 2010-2017
CS	Declares no conflict of interest.	Declares no conflict of interest
GC	He was a consultant and speaker, and received research funding and scientific sponsorship.	Pfizer S.A.S, Merck Sharp and Dohme (MSD), Procaps, Colombian Association of Infectology (ACIN), Pan American Health Organization (PAHO), Sanofi. 2015-2016
EM	He was a consultant and speaker, and received research funding and scientific sponsorship.	Pfizer S.A.S, Merck Sharp and Dohme (MSD), Stendhal, Gilead/Gador, GSK, ABBVIE. 2015-2017
WC	He was a speaker and received scientific sponsorship.	Pfizer S.A.S, Sanofi. 2016-2017
EL	He was a speaker and received scientific sponsorship.	Pfizer S.A.S, Astellas, Takeda, Stendhal. 2016-2017
GR	He was a consultant and speaker, and received research funding and scientific sponsorship.	Pfizer S.A.S, Merck Sharp and Dohme (MSD). 2014-2017
IB	He was a speaker and received scientific sponsorship.	Merck Sharp and Dohme (MSD), Procaps. 2016-2017
IZ	She received scientific sponsorship.	Procaps. 2017
ZL	She received scientific sponsorship.	Pfizer S.A.S, Sanofi. 2016-2017
JA	Declares no conflict of interest.	Declares no conflict of interest
AR	Declares no conflict of interest.	Declares no conflict of interest
CA	He was a speaker, and received research funding and scientific sponsorship.	Merck Sharp and Dohme (MSD), Procaps. 2016-2017
JV	He was a consultant and speaker, and received research funding and scientific sponsorship.	Pfizer S.A.S, Merck Sharp and Dohme (MSD). 2015-2017
JC	He was a consultant and speaker, and received research funding and scientific sponsorship.	Pfizer S.A.S, Merck Sharp and Dohme (MSD). 2015-2017
СМР	Declares no conflict of interest.	Declares no conflict of interest

Annex 4. Table of conflict of interest disclosed by authors

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Annex 5. Recommendations for the identification of yeast-like specie⁴³.

Identification of Candida species

- As a minimum requirement, colony micromorphology observation complemented by macromorphology using the CHROMagar Candida® medium, is recommended.
- For second-level hospitals, it is recommended that one or more of the methods below should be used for the identification of species:
 - o Micromorphology of the colonies.
 - o Macromorphology (CHROMagar Candida® medium).
 - o Biochemical tests:
 - □ In-house conventional methods.
 - □ Manual commercial systems with limited databases (e.g. Auxacolor® or Uni-Yeast Tek®).
- For third-level hospitals, where transplant recipients, hematological and/or immunocompromised patients are treated, the following are recommended as minimum requirements:
 - o Micromorphology complemented by biochemical tests (API 20 C AUX®, API ID32C®, YST Vitek 2®, RYI MicroScan® or Yeast ID Panels®).
 - o Molecular methods in specific situations.
 - Molecular methods (PCR and MALDI-TOF) should be considered for the identification of emerging pathogens and when investigating outbreaks of fungal infections.

Adapted from: Colombo AL et al⁴³.

PCR: Polymerase chain reaction; MALDI-TOF MS: Matrix assisted laser desorption ionization Time-of-Flight.

Annex 6. Chromogenic media for the identification of Candida species⁴³.

Characteristics of colonies per species after incubation in CHROMagar <i>Candida</i> ® medium, at 37 °C, for two days					
Species Color and morphology					
Candida albicans	Green.				
Candida tropicalis Dark blue to grey blue (with pink halo in agar).					
Candida krusei	Pale pink to purple (intense tone with pale edges) and a dry texture.				

Adapted from: Colombo AL et al⁴³.

Annex 7. Automated methods for the identification of yeast-like fungus species

Method*	Basis	Comment
YST Vitek 2 [®] cards	Analysis cards with 63 wells for the detection of fungal metabolism Reading by fluorescence.	Identification of 51 yeast-like species and organisms, including <i>Candida</i> <i>dubliniensis.</i> Requires additional tests (mainly morphological) when the identification has low discrimination. Time to identification: 15 hours
YT MicroPlate® system	Identification panels with 94 biochemical tests	Identifies up to 267 different species belonging to 53 genus Time to identification: up to 72 hours
RYI MicroScan® panel	Microdilution plate with 96 wells that uses 27 dehydrated substrates Identification is performed by conventional and chromogenic tests	Rapid identification of 40 yeast-like species and organisms May require additional tests (mainly morphological) when the identification has low discrimination. Time to identification: 4 hours
Yeast ID ® Panel	Identification panels based on conventional biochemical, chromogenic and fluorogenic tests.	Identification of 64 species of yeast and yeast-like organisms Requires establishing the source culture medium of the fungal isolate in order for the determination of secondary morphological characteristics Time to identification: 16 hours

*Information taken from the manufacturer package inserts.

Annex 8. Considerations on in vitro antifungal susceptibility commercial tests²⁵⁸.

nex 8. Considerations on in vitro antifungal susceptibility commercial tests ²⁵⁹ .	
 FB Fungus (bioMérieux), is based on the CLSI microdilution method. Applicable for <i>Candida</i> spp. and <i>Cryptococcus neoformans</i> It is an easy to perform, reproducible and affordable technique. It has a good consistency with reference methods (CLSI-EUCAST), mainly with amphotericin B and 5-fluorocytosine. Limitations Does not include echinocandins There are discrepancies between fluconazole and itraconazole 	
 ST-YS01 Vitek® 2 (bioMérieux), is based on the CLSI microdilution method. Applicable for <i>Candida</i> spp. and <i>C. neoformans</i>. Is an automated and easy technique that allows determining the MIC. It has a good consistency with reference methods (CLSI-EUCAST). Limitations There are discrepancies when testing antifungal agents with uncommon yeast isolates. It does not include all echinocandins nor itraconazole. 	
ensititre [™] YeastOne [™] (Trek Dg. System) is a colorimetric dilution method based on the CLSI microdilution method. It incorporates Alamar blue, an oxidoreductase dye that turns red when there is growth and remains blue when there is no growth. Good reproducibility. One advantage is a more objective reading because turbidity should not be read but only the change in color. Limitations ^o Color change may be difficult to appreciate in some isolates. ^o Paradoxical effect (growth in concentrations above MIC) is common with itraconazole and echinocandins.	
eo-Sensitabs™ (Rosco Diagnostic) and SensiDisks (Bio-Rad), are tablets containing the antifungal agent in crystallized form. Its main advantage is the blets (up to 4 years at 4-8°C). They are an inexpensive, reproducible and easy to perform resource in routine laboratory tests. They are useful for knowing the susceptibility to systemic antifungal agents. Limitations ^o Issues with azole readings: presence of colonies inside the halo. ^o Issues with the interpretation of some isolates. ^o High percentage (>5%) of errors with fluconazole (some resistant isolates were identified as susceptible).	ne stability of the
test® (bioMérieux) and MIC [™] (Oxoid), are quantitative systems of diffusion in agar that allow the determination of MIC. Applicable for <i>Candida</i> sp and filamentous fungi. They are rapid, reproducible techniques that allow the determination of MIC. They are useful for the determination of filamentous fungi in vitro susceptibility Limitations ^o Subjectivity and difficulty in yeasts and filamentous fungi MIC readings	p., C. neoformans

Adapted from: Rivas P et al²⁵⁸.

CLSI: Clinical and laboratory standards institute; EUCAST: European committee on antimicrobial susceptibility testing; MIC: Minimum inhibitory concentration.

e ·	Antifungal	Cut off points, µg/mL'						
Species	agent	S	DDS	I	R			
	Fluconazole	≤2	4		≥8			
	Itraconazole	≤0.12	0.25-		≥1			
			0.5					
	Voriconazole	≤0.12		0.25-	≥1			
C. albicans				0.5				
	Posaconazole							
	Anidulafungin	≤0.25		0.5	≥1			
	Caspofungin	≤0.25		0.5	≥1			
	Micafungin	≤0.25		0.5	≥1			
	Fluconazole		32		≥64			
	Itraconazole							
	Voriconazole							
C. glabrata	Posaconazole							
	Anidulafungin	≤0.12		0.25	≥0.5			
	Caspofungin	≤0.12		0.25	≥0.5			
	Micafungin	≤0.06		0.12	≥0.25			
	Fluconazole	≤2	4		≥8			
	Itraconazole							
	Voriconazole	≤0.12		0.25-	≥1			
С.				0.5				
parapsilosis	Posaconazole							
	Anidulafungin	≤2		4	≥8			
	Caspofungin	≤2		4	≥8			
	Micafungin	≤2		4	≥8			

Annex 9. Clinical cut off points for common antifungal agents againstCandida species^{38,55}.

	Antifungal	Cut off points, µg/mL'						
Species	agent	S	DDS	I	R			
	Fluconazole	≤2	4		≥8			
	Itraconazole							
	Voriconazole	≤2	4		≥8			
C. tropicalis	Posaconazole							
	Anidulafungin	≤0.25		0.5	≥1			
	Caspofungin	≤0.25		0.5	≥1			
	Micafungin	≤0.25		0.5	≥1			
	Fluconazole							
	Itraconazole							
	Voriconazole	≤0.5		1	≥2			
C. krusei	Posaconazole							
	Anidulafungin	≤0.25		0.5	≥1			
	Caspofungin	≤0.25		0.5	≥1			
	Micafungin	≤0.25		0.5	≥1			

Adapted from: Pappas PG et al.; Albataineh MT et al^{38,55}.

Blank spaces mean that there are insufficient data to establish clinical cut off points.

l: intermediate; MIC; Minimum Inhibitory Concentration; R: Resistant; S: Susceptible; DDS: Dose-Dependent Susceptible.

*CLSI clinical cut off points adopted by CLSI.

Image: constraint of the second sec	Anamorph stage	Telemorph stage	Clinical relevance and particularities
C. aprecial It is probably less pathogenic than C. albicans and were found almost exclusively in female urinary tract samples. C. auris Post described Related to C. hormalonii. C. duris Post described Cashy related to C. gliborato. C. dubitonio. Trichomonacos clerrii Uncertani. dirical significance. C. dubitonio. Post described Cashy related to C. dubicons. C. dubitonio. Not described Cashy related to C. dubicons. Mith an intrinsic susceptibility pattern is iniliar to that of the abovementioned species; however, i has the potential for acquired resistance. C. fabianii Cyberlindnera fabianii Uncertani. divisia significance. FG Mithain Megrecaryma guillermandrii. Casey related to C. fabicons. C. guillermondii Megrecaryma guillermandrii. Casey related to C. fabicons. C. guillermondii Megrecaryma guillermandrii. Casey related to C. farmalina and same regions in Asia. C. guillermondii Megrecaryma guillermandrii. Calicons. Magrecaryma guillermandrii. <		Not described	Closely related to C. albicans.
It is probably less pathogene than C. ablcons and were found almost exclusively in termale unhary tract samples. C. auris Not described Related to C. <i>hermulanii</i> . C.2 MC is higher than that of C. ablcons. Multi-resistant species and very durable in the environment. Resistant to the usual hospital disintectants. C. broccenensis Not described Cosley related to C. <i>globrata</i> . It is saceptibility pattern is similar to that of C. globrata thigh azole MIC compared with that of C. ablcines. C. dipersit Trichomonoscus coformi Uncertain clinical significance. Inherent resistance to several antifungal agents. C. dipleriti Outeschool Distribution of the abovementioned species; however, i has the potential for acquired resistance. C. fabianii Uncertain clinical significance. Inferent resistance constructs of general antifungal agents. C. fabianii Mut described Uncertain clinical significance. C. fabianii Patho proteinal analysis. Distribution and a second and the acquired resistance. C. fabianii Meterating agents an uncomon fungenia causing agent. Resett data question whether this species is a human pathogen (it does not grow at 37°C and there are no cause consortimed by equeving analysis. C. fabianii Meyercogram guillermootiii Coles (related to C. ablcons C. fabianii Meyercogram guillermootiii Coles (related to C. ablcons	C africana		This species exhibits an intrinsic susceptibility pattern.
C. auris Not described Related to C. <i>homoloxii</i> . C.2 XMC is higher than that of C. <i>ablicans</i> . Multi-resistant species and very durable in the environment. Resistant to the usual hospital dialintecants. C. bracerensis Not described Closely related to C. <i>fabrants</i> . Its susceptibility pattern is similar to that of C. glabrata (c. dubtan). C. diferrii Trichomonexce clerrii Uncertain clinical significance. <i>C. dubtania</i> . C. diblininsis Not described Closely related to C. <i>ablicans</i> . With an intrinsic susceptibility pattern is imilar to that of the abovementioned species; however, it has the potential for acquired resistance. C. fabianii Cyberlindneer abalanii Uncertain clinical significance. ICZ MiC is higher than that of C. <i>ablicans</i> . C. glatiantia Observation susceptibility pattern is similar to that of the abovementioned species; however, it has the potential for acquired resistance. Discrepticities accounting agent. Recent data question whether this species is a human pathogen (d does not grow at 37C and there are no cases confirmed by equirening analysis. C. guillermondii Meyerozyma guillermondii Observations and accent the timb. C. auditaria May be a human pathogen ad accent to itagin there are no cases confirmed by equirening analysis. May be a human pathogen induces infections and central wnous catheter humania. C. glatilermondii Moy described May be a human pathogen ad respinatory infections caused	c. upricuna		It is probably less pathogenic than C. albicans and were found almost exclusively in female
C. auris FCZ MIC is higher than that of C ablcons. Multi-resistants species and very durable in the environment. Resistant to the usual hospital disinfertants. C. bracerensis Not described Closely related to C globrato. It is susceptibility pattern is similar to that of C globrato (high azole MIC compared with that of C ablcons). C. dubliniensis Trichomonaccu ciperrii Uncertain clinical significance. Inherent resistance to several antifungal agents. C. dubliniensis Not described Closely related to C ablcons. With an intrinsic susceptibility pattern is similar to that of the abovementioned species, however, i has the potential for acquired resistance. C. fobianii Cyberlinhera fabianii Pecerat data cuestion whether the species is a nucormon fungemia-causing agent. Recent data cuestion whether the species is a nucormon fungemia-causing agent. Recent data cuestion whether the Species is a nucormon fungemia-causing agent. Recent data cuestion whether the Species is a nucormon fungemia-causing agent. Recent data cuestion whether the Species is a nucormon fungemia-causing agent. Recent data cuestion whether the Species is a nucormon fungemia-causing agent. Recent data cuestion whether the Species is a nucormon fungemia-causing agent. Recent data cuestion whether the Species is a nucleotion statistic. Species and AB MIC is high. Related to C. anvis C hotemulonii (including) Not described Closely related to C. anvis C hotemulonii Species and species the species of fungemia and respiratory infections caused by this species. Related to C. anvis C hotemulonii Species and species fungemia admeteripriatory infections caused by this species. Related to C. anvis			urinary tract samples.
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C. bracerensis Not described Clogely related to C. globrate. Its susceptibility pattern is similar to that of C. globrate (high azole MIC compared with that of C. ablicans) C. citerrii Trichomonacus ciferrii Uncertain clinical significance. Inherent restance to several antitugal agents. C. dobiniensis Not described Closely related to C. ablicans. With an initia's susceptibility pattern similar to that of the abovementioned species; however, i has the paternial for acquired restance. C. fabianti Cyberlundnera fabrani (C. globrani) Closely related to C. ablicans. C. fabianti Cyberlundnera fabrani (C. globrani) This species is an uncommon fungemia-causing agent. Recent data question whether this species is a human pathogen (it does not grow at 37°C and there are no cases confirmed by sequencing analysis). C. guiltermondii Meyerozyma guillermoniii Closely related to C. ablicans. Has the companies of the abovemention of species is a human pathogen science in the species. Acades and AB (it is high Related to C. auxis. C. hellenica Ziggooscus meyeros There have beer reports of fungemia and respiratory infections caused by this species. Reduced susceptibility to FZ, TZ and CAS. It is susceptible to FZZ. C. intermedia Not described It is an oropharingeal colonization agent associated with blockstream infections and peritoritit it is susceptibility to FZZ. TZ and CAS. It is susceptibility to FZZ. C. intermedia Not described	e. uurt5		
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Adapted from Arendrup MC et al¹⁰.

MIC: Minimum inhibitory concentration; FCZ: Fluconazole; AB: Amphotericin B; ITZ: Itraconazole; CAS; Caspofungin; VCZ: Voriconazole; 5FC: 5-Flucitosine.

Diagnostic Test	Description	Optimal sample	S (%)	Sp (%)	Comments and interpretation
Mannan and Anti- Mannan Platelia™ <i>Candida</i> Ag Plus® Platelia™ <i>Candida</i> Ab Plus® (Bio-Rad Laboratories)	ELISA for the detection of <i>Candida</i> spp. Abs. and Ags.	Serum and plasma	54-94	59-95	It yields results 6 days earlier than detection in blood cultures, even though its use as an early marker of IC is still uncertain. High susceptibility to most of the species; it is not reliable for the detection of certain species such as C. <i>parapsilosis</i> o C. <i>guilliermondii</i> . PPV 17-94%; NPV 89-94%. Its high NPV makes it a good alternative disease exclusion test, which would avoid unnecessary antifungal treatment. Interpretation of results: A negative MN Ag. result does not exclude the diagnosis of IC, mannanemia is a short-term condition. Anti-MN-Ab and MN Ag titers are supplementary. Serum of patients at risk of IC without MN-Ag may have high titers of anti-MN-Ab and vice-versa.
 (1,3)-β-D-glucan Fungitell (Associates of Cape Cod Inc., USA). Wako WB003 (Wako Pure Chemical Industries, Japan). Fungitec G (Seikagaku Kogyo Corporation, Japan). B-G Star (Maruha Corporation, Japan). 	ELISA for the detection of (1,3)-β-D-glucan, a panfungal component of the cell wall	Serum	65-81	57-83	Is a panfungal <i>Candida</i> non-specific marker. It yields results 7 days earlier than detection in blood cultures. Its diagnostic usefulness varies and depends on the studied population of patients. PPV 22-63%; NPV 77-96%. It is considered particularly useful in patients with intraabdominal infections, in whom culture sensitivity is reduced. Interpretation of results: Optimal results are obtained when two consecutive tests are positive. One positive result does not allow the identification of the species causing the infection.
CAGTA Candida albicans IFA IgG® (Vircell, Spain)	Indirect immunofluorescence assay based on the detection of antibodies against <i>C.</i> <i>albicans</i> germ tube surfaces	Serum	77-89	91-100	There is a correlation between a positive test and proven IC. CAGTA is not affected by <i>Candida</i> colonization or antifungal treatment. It is useful in the diagnosis of <i>Candida</i> -deep seated infections. Using an early CAGTA detection based-approach may reduce the mortality of critical patients at risk of IC, especially in surgical patients. Interpretation of results Positive in IC caused by: <i>C. albicans, C. tropicalis, C. parapsilosis,</i> <i>C. krusei, C. glabrata, C. guilliermondii, C. dubliniensis.</i>

Annex 11. Serum biomarkers for the diagnosis of candidemia/IC^{37,41,56,57}.

Adapted from: Arvanitis M et al.; León C et al.; Ayats J et al.; Colombo AL et al^{37,41,56,57}.

ELISA: Enzyme-linked immunosorbent assay; Ab: Antibody; Ag.: Antigen; S: Sensitivity; Sp: Specificity; PPV: Positive Predictive Value; NPV: Negative Predictive Value; MN: Mannan; BD: (1,3)-β-D-glucan; CAGTA: Anti-mycelium antibodies.

Annex 12. Available molecular and proteomic biomarkers for the diagnosis of candidemia/IC^{37,39,55,66,68}.

Test	Basis	Optimal sample	S (%)	Sp (%)	Comments and interpretation
LightCycler SeptiFast™ (Roche, Germany)	Multiplex PCR for the detection of bacteria and fungi DL: 30–100 CFU/mL	Clinical samples or samples of negative cultures	61	99	It is possibly less susceptible for <i>Candida</i> spp. compared with similar tests It has better susceptibility compared with conventional blood cultures It is supplementary for diagnosis in high-risk patients Interpretation of results: It is able to rapidly and accurately exclude the possibility for candidemia and, therefore, limits the inadequate use of antifungal agents Detected species: <i>C. albicans, C. tropicalis, C. krusei, C.</i>
FilmArray blood culture identification (Film-Array [™] - BioFire DX) (bioMerieux)	Nested PCR Multiplex	Positive blood culture	95-100	99.5-100	parapsilosis, C. glabrata. It requires minimum preparation of the sample It has a quick turnaround time It requires the use of specialized equipment Interpretation of results: It is able to rapidly and accurately exclude the possibility for candidemia and, therefore, limits the inadequate use of antifungal agents Detected species: C. albicans, C. tropicalis, C. krusei, C. parapsilosis, C. glabrata.
T2 Candida (T2Biosystems Inc)	NAAT followed by hybridization and T2 magnetic resonance assay DL: 1-3 CFU/mL	Whole blood	91	98	It requires minimum preparation of the sample It has a low limit of detection NPV ≈100% It is expensive and requires the use of specialized equipment Interpretation of results: Even though this test has the potential to significantly improve IC diagnosis and management, additional evaluations are required to determine a more profitable implementation. It is able to rapidly and accurately exclude the possibility for candidemia and, therefore, limits the inadequate use of antifungal agents Detected species: <i>C. albicans, C. tropicalis, C. krusei, C. parapsilosis, C. glabrata.</i>
PNA FISH (Yeast Traffic Light PNA FISH™)	Nucleic acid sequence probes for the detection of <i>C. albicans/C.</i> <i>parapsilosis, C.</i> <i>glabrata/C. krusei</i> or <i>C. tropicalis</i>	Positive blood culture	92-100	95-100	It is very susceptible and specific It has a quick turnaround time Interpretation of results: It is able to rapidly and accurately exclude the possibility for candidemia and, therefore, limits the inadequate use of antifungal agents Detected species: C. albicans/ C. parapsilosis; C. tropicalis; C. krusei/C. glabrata.
MALDI-TOF MS (bioMerieux, France or Bruker Daltonics, Germany)	Concentration of yeast sediment followed by MALDI- TOF MS mass spectrophotometry analysis	Positive cultures or directly from clinical samples, including positive blood cultures	0-100	¿?	The reports on its performance vary, probably due to differences in the preparation of samples (Sepsityper vs. <i>in-house</i> methods) It is convenient for laboratories that use equipment already Interpretation of results: Detected species: multiple species, depending on the spectra available on libraries
PCR/ESI-MS (Iridica™, Abbott, USA)	PCR followed by electrospray ionization - mass spectrometry Amplicon (PCR/ ESI-MS)	Positive cultures or directly from clinical samples, including positive blood cultures	83	94	High susceptibility and specificity It is expensive and requires the use of specialized equipment Interpretation of results: Detected species: multiple species

Adapted from: Arvanitis M et al.; Brady AC et al.; Vanichanan J et al.; Powers-Fletcher MV et al.; Albataineh MT et al^{37,39,55,66,68}.

DL: Detection Limit; S: Sensitivity; Sp: Specificity; (%): Percentage; NAAT: Nucleic acid amplification test; PNA FISH: Fluorescent *in situ* hybridization using peptide nucleic acid; MALDI-TOF MS: Matrix assisted laser desorption ionization time-of-flight; PCR/ESI-MS: PCR + mass spectrometry + electrospray ionization.

C_{max}

AUC_{24h}

Protein binding

T 1/2

Pharmacokinetics

11%

6 mg/L with 100 mg OA; 20-30

412 mg x h/L with 400 mg/day IV. 30 h, 18 h in children (there are no

data in severe kidney failure)

mg/L with 400 mg OA

ungal

Fluconazole

ent

Annex 13. Pharmacokinetics/Pharmacodynamics of Systemic Antifungal Agents^{65,124,149,148,150,151}.

Antifungal agent		Pharmacokinetics				tifur ager
	ıgin	C _{max}	12 mg/L (with 50 mg IV.)			
		AUC _{24h}	75 mg x h/L (with 50 mg/day IV.)			
	Caspofungin	T 1/2	9-11 h			
	Casp	Protein binding	97%			
		DV	0.3 L/kg			
s		C _{max}	7.2 mg/L (with 100 mg IV.)			
ECHINOCANDINS	Anidulafungin	AUC _{24h}	105 mg x h/L (with 100 mg/day IV.)			
DCAI	ılafu	T 1/2	26 h	-		
NIH	Anidu	Protein binding	99%			
B		DV	0.56 L/kg			
		C _{max}	7 mg/L (with 100 mg IV.)			
	gin	AUC _{24h}	103 mg x h/L (with 100 mg IV.)			
	Micafungin	T 1/2	15 h		AZOLES	
	Mica	Protein binding	>99%		AZC	
		DV	0.3 L/kg			
	Amphotericin B deoxycholate	C _{max}	2 mg/L (with 50 mg IV.)			
		AUC _{24h}	17 mg x h/L (with 50 mg IV.)			
		T 1/2	24 h			
		Protein binding	>90%			
		DV	4 L/kg			
	Liposomal amphotericin B	C _{max}	80 mg/L (with 5 mg/kg/day IV.)			
NES		AUC _{24h}	555 mg x h/L (with 5 mg/kg/day IV.)			F
POLYENES		T 1/2	24-30 h			
PC		Protein binding	90%			
		DV	0.15 L/kg			
	Amphotericin B lipid complex	C _{max}	1.7 mg/L (with 5 mg/kg/day IV.)			
		AUC _{24h}	14 mg x h/L (with 5 mg/kg/day IV.)			SINE
		T 1/2	19-45 h			YTOS
	umph lipid	Protein binding	90%	FLUCYTOSINE		
		DV	130 L/kg			

				Frotein binding	1170
ng IV.)				DV	0.6-0.8 L/kg
00 mg/day IV.)			e	C _{max}	0.25-1 mg/L with 200 mg OA; 1.9 mg/L with 200 mg OA
			ltraconazole	AUC _{24h}	15 mg x h/L with 200 mg/day IV.
			acon	T ^{1/2}	20-42 h
			Itra	Protein binding	99%
g IV.)				DV	9 L/kg
00 mg IV.)		AZOLES	le	C _{max}	3-6 mg/L with 4 mg/kg IV.; 2-3 mg/L with 200 mg OA (both in steady state)
		AZC	lazo	AUC _{24h}	16 mg x h/L with 4 mg/day IV.
			Voriconazole	T 1/2	6 h (there are no data in severe kidney failure)
IV.)				Protein binding	60%
) mg IV.)				DV	4.6 L/kg
			a	C _{max}	0.22 mg/L
			azolo	AUC _{24h}	7.7-33.8 mg x h/L
			Posaconazole	T ^{1/2}	35 h
/kg/day IV.)			Posa	Protein binding	98-99%
				DV	4.9-18.8 L/kg
mg/kg/day			e	C _{max}	7.2 mg/L
			azol	AUC _{24h}	121.4
			loon	T ^{1/2}	130
			lsavuconazole	Protein binding	99%
			-	DV	450 L
/kg/day IV.)				C _{max}	45 mg/L with 2 g OA
mg/kg/day IV.)			INE	AUC _{24h}	825 mg x h/L with 6 g/day IV.
		JCYTOSINE		T 1⁄2	3-5 h (in severe kidney failure: 200 h)

Protein binding

DV

< 10%

0.6 L/kg

Adapted from: Mensa-Pueyo J. et al.; Gilbert DN et al.; Ruiz-Camps I. et al.; Cuenca-Estrella M; Lewis RE; Bellmann R et al^{65,124,149,148,150,151}.

C_{max}: Maximum concentration (Serum peak concentration); AUC_{24h}: Area under the curve (total drug, including that bound to proteins) 24h; T^{1/2}: Elimination halflife; DV: Distribution volume; MEC: Minimum effective concentration; MIC: Minimum inhibitory concentration; h: Hours; g: Grams; min: Minutes; IV.: Administered intravenously; OA: Oral administration; kg: Kilogram; L: Liter; mEq: Milliequivalent; g: gram; min: Minutes; SOT: Solid organ transplant; HPCT: Hematopoietic progenitor cells transplant; CNS: Central nervous system.

Annex 14. Antifungal treatment per isolated Candida species.

Species	Antifungal agent of choice	Alternative agent	Comments	
C. albicans In neutropenic or critical patients: Echinocandin, standard dose. In non-neutropenic, stable patients: FCZ (800 mg loading dose, then 400 mg daily).		AmB-D or AmB-L, standard dose.	Depending on the susceptibility and after appropriate clinical/microbiological response is achieved, de-escalation to FCZ (800 mg loading dose, then 400 mg daily) or VCZ	
C. parapsilosis	In neutropenic or critical patients: Echinocandin, standard dose. In non-neutropenic, stable patients: FCZ (800 mg loading dose, then 400 mg daily).	AmB-D or AmB-L, standard dose.	(6 mg/kg twice daily for 2 doses, then 3 mg/kg twice daily) may be appropriate, if echinocandin were used as the starting therapy.	
C. tropicalis In neutropenic or critical patients: Echinocandin, standard dose. In non-neutropenic, stable patients: FCZ (800 mg loading dose, then 400 mg daily).		AmB-D or AmB-L, standard dose.		
C. auris*	AmB-L (3 mg/kg daily) for 5 d + Equinocandin, standard dose, for 3 weeks.	Not established.		
C. glabrata	Echinocandin, standard dose.	AmB-D or AmB-L, standard dose.		
C. krusei	Echinocandin, standard dose.	AmB-D or AmB-L, standard dose.	Depending on the susceptibility de- escalation to VCZ (6 mg/kg twice daily for 2 doses, then 3 mg/kg twice daily) may be appropriate.	
C. lusitaniae	FCZ (800 mg loading dose, then 400 mg daily). VCZ (6 mg/kg twice daily for 2 doses, then 3 mg/kg twice daily).	Echinocandin, standard dose.		
C. guilliermondii	Echinocandin, standard dose.	AmB-D or AmB-L, standard dose.	Depending on the susceptibility and after appropriate clinical/microbiological response is achieved, de-escalation to FCZ (800 mg loading dose, then 400 mg daily) or VCZ (6 mg/kg twice daily for 2 doses, then 3 mg/kg twice daily) may be appropriate.	
C. haemulonii Not established.		Not established.	High FCZ and AmB-D in vitro MICs, with good echinocandin activity; however, published evidence is insufficient.	

(Adapted by experts of the consensus)

*https://www.cdc.gov/fungal/diseases/candidiasis/c-auris-treatment.html. Take into account the hemodynamic situation of the patient and the in vitro sensitivity of the specific isolation, for the start of combined treatment.

FCZ: Fluconazole; VCZ: Voriconazole; AmB-D: Amphotericin B deoxycholate; AmB-L: Liposomal amphotericin B; CAS: Caspofungin; ANI: Anidulafungin; MIC: Micafungin; Day/days; h: Hours; mg: Milligrams; kg: Kilograms.

Annex 15. PK/PD Parameters of Antifungal Agents^{65,124}.

Antifungal agent	In Vitro Activity	In Vitro PAE	Efficacy Predictive Parameters
Polyenes	Fungicidal	Long-term	C _{max} /MIC: 4-10
(Amphotericin B)	Concentration-dependent against Candida	Concentration-dependent against	
	spp., Cryptococcus and Aspergillus spp.	yeasts and filamentous organisms.	
Triazoles	Fungistatic	Long-term	AUC/MIC: ≥25 against Candida spp.
(Fluconazole,	Concentration-dependent against Candida	Time- and concentration-dependent	
Itraconazole,	spp. and Cryptococcus spp.	against Candida spp. and	C _{min} : > 500 against <i>Aspergillus</i> spp. with
Voriconazole,		Cryptococcus spp. but not against	Itraconazole and Voriconazole
Posaconazole)	Fungistatic	filamentous organisms.	
	Time- and concentration-dependent		Posaconazole requires plasma concentration:
	against Aspergillus spp.		1000-1500 mg/L
Echinocandins	Fungicide	Long-term	C_{max} /MIC: > 4 against <i>Candida</i> spp.
(Caspofungin,	Concentration-dependent against Candida	Concentration-dependent against	
Anidulafungin,	spp.	Candida spp.	AUC/MIC: > 250 in tissue and plasma
Micafungin)			
	Fungistatic		C _{max} /MEC (effective): 10 against Aspergillus
	Concentration-dependent against		spp.
	Aspergillus spp.		

Adapted from: Lewis RE; Bellmann R et al^{65,124}.

PAE: Post-antifungal effect.

Annex 16. Candida species and predisposing factors for IFD in pediatric patients¹⁸⁹.

Species	Risk Factor for IFD
C. albicans	Intensive Care Units, CVC, treatment with antibiotics or corticosteroids, surgery
C. parapsilosis	Prematurity, CVC, PN
C. tropicalis	Immunosuppression, neoplastic diseases
C. glabrata	Prior treatment with FCZ, severe immunosuppression
C. krusei	Prior treatment with FCZ, immunosuppression, neoplastic diseases

Adapted from: Figueras C et al¹⁸⁹.

CVC: central venous catheter; PN: Parenteral nutrition: FCZ: Fluconazole.

Annex 17. Algorithm of antifungal prophylaxis with fluconazole in preterm neonates⁹⁸.

High-risk groups	< 1000 g at birth or born < 27 weeks	1000-1500 g at birth
Criterium	< 5 days of age CVC or endotracheal tube	 > 3 days of therapy with antibiotics CVC
Dose	3 mg/kg IV. (twice a week)	3 mg/kg IV. (twice a week)
Duration	Until the patient no longer requires venous access	Same as that of treatment with antibiotics, or while the CVC is in place
Monitoring	Weekly liver function tests All isolates should undergo susceptibility tests	Weekly liver function tests All isolates should undergo susceptibility tests
Empiric treatment of <i>Candida</i> invasive infections	AmB	AmB
Level of evidence	A-I	B-II

Adapted from: Kaufman DA98.

Al and BII abbreviations refer to the level of evidence/degree of standard recommendation.

CVC: Central Venous Catheter; IV.: Administered Intravenously; AmB: Amphotericin B.